

NONTECHNICAL ABSTRACT

Interleukin-2 (IL2) is a protein product of activated lymphocytes which has been shown in animal studies to produce tumor regression by enhancing immune responses directed against tumor cells. The recombinant IL2 protein has been administered to patients with advanced cancer, but has been found to be toxic at high doses which limited its clinical efficacy.

We have previously studied the use of gene therapy with an adenoviral vector expressing the Herpes Simplex Virus thymidine kinase (HSV-tk) gene in animals as well as patients with metastatic cancer to the liver. In these studies, the vector (Adv.RSV-tk) was administered by intratumoral injection into one metastatic tumor in the liver, and followed by systemically administered ganciclovir, a prodrug which is converted by the HSV-tk into toxic products which produces cell death. We have found in a Phase I trial in patients with metastatic colorectal cancer to the liver that intratumoral injection of Adv.RSV-tk was well tolerated without serious toxicities (BBIND #6906, ORDA #9610-164)..

In our studies with mice bearing established colon cancer in the liver, we found that combining Adv.RSV-tk with a second adenoviral vector expressing the murine interleukin-2 gene (Adv.RSV-mIL2), delivering the mixture by intratumoral injection, and following with ganciclovir, was significantly more effective in producing tumor regression, antitumor immunity, and survival prolongation than either vector alone.

We have translated these preclinical findings into a Phase I/IB trial of Adv.RSV-hIL2 in escalating doses combined with Adv.RSV-tk at a fixed dose found to be safe from our previous Phase I trial of Adv.RSV-tk. Intravenous ganciclovir will be administered following the vector injection in the same dose and schedule as the previous Phase I trial. The intratumoral injection is performed by percutaneous insertion of up to three skinny needles through the skin into one liver tumor under ultrasound guidance. We will assess the safety of the treatment. We will also collect data on the effectiveness of the treatment in producing tumor regression and in inducing immune responses. To determine if the study treatment was successful in inducing immune responses against the patient's tumor, we will obtain a sample of the tumor prior to the study treatment by laparoscopy. The tumor specimen will be used to test the patient's lymphocytes for antitumor immunity following treatment and for preparing a sample for skin testing.

Clinical grade Adv.RSV-hIL2 and Adv.RSV-tk have been produced for use in the proposed clinical trials by the University of Pennsylvania Institute for Human Gene Therapy under the National gene vector Laboratory Award Program, and by the Baylor College of Medicine Gene Vector Laboratory, respectively.